Human Leukocyte Antigen and Clinical and Demographic Characteristics in Psoriatic Arthritis and Psoriasis in Chinese Patients

HSIEN-TZUNG LIAO, KUAN-CHIA LIN, YUN-TING CHANG, CHUN-HSIUNG CHEN, TOONG-HUA LIANG, WEI-SHENG CHEN, KUEI-YING SU, CHANG-YOUH TSAI, and CHUNG-TEI CHOU

ABSTRACT. ***Objective.*** Psoriasis and psoriatic arthritis (PsA) are interrelated disorders. To date, no study has compared the differences of genes between patients with PsA and psoriasis and healthy controls in a Chinese population. We conducted a retrospective study to determine the human leukocyte antigen (HLA) -A, -B, -Cw, -DR, and -DQ alleles in Chinese patients with PsA and psoriasis.

Methods. HLA studies were performed using polymerase chain reaction sequence-specific oligonucleotide (PCR-SSO) genotyping methods in 91 patients with PsA and 80 with psoriasis and 75 controls. Age at disease onset, sex, disease duration, enthesitis, and uveitis were also analyzed.

Results. Among the patients with PsA and psoriasis, the frequency of HLA-B27 was significantly higher in PsA and HLA-A*30, -Cw*06, -DR*07 in psoriasis compared with controls. In contrast, HLA-B*58 was more common in controls than in PsA and psoriasis groups, and the prevalence of HLA-DR*17 was significantly higher in controls than in those with psoriasis. Comparing PsA and psoriasis, the prevalence of HLA-B*27 and HLA-Cw*12 were more common in PsA patients, while the prevalence of HLA-DR*07 was higher in those with psoriasis ($p < 0.05$). Among PsA patients, the association between HLA-B*27 and axial joint involvement and uveitis was significant ($p < 0.05$).

Conclusion. Certain HLA alleles are found in Chinese patients with psoriasis (HLA-A*30, -Cw*06, -DR*07) and PsA (HLA-B*27). Psoriasis patients with the HLA-B*27 and/or -Cw*12 may have higher risk of developing PsA. Ours is the first study to assess the genetic role of HLA in patients with psoriasis and PsA in a Chinese population. (First Release Mar 15 2008; J Rheumatol 2008;35:891–5)

Key Indexing Terms:
PSORIATIC ARTHRITIS PSORIASIS HUMAN LEUKOCYTE ANTIGEN GENETIC STUDY

Genes of the major histocompatibility complex (MHC) or human leukocyte antigen (HLA) have been mapped to chromosome 6p21.3[1,2]. They encode a series of glycoproteins that play an important part in immunological self/non-self discrimination by presenting antigens to T cells[3]. It is known that some rheumatic and autoimmune diseases are associated with HLA genes. Psoriasis is a chronic inflammatory disease that affects 1% to 3% of the Caucasian population. However, the prevalence of psoriasis in Chinese was 0.12% and psoriatic arthritis (PsA) was about 5% of patients with psoriasis[4,5]. The skin pathology reveals keratinocyte hyperproliferation and recruitment of T lymphocytes and mononuclear cells in the affected skin[6]. PsA is an inflammatory arthritis that affects 20%–30% of patients with psoriasis. Accumulating evidence indicates that PsA and psoriasis are multifactorial disorders caused by the concerted action of multiple disease genes in a single individual, triggered by environmental factors. Some of these genes control the severity of diseases by regulating inflammation and immunity, whereas others are unique to PsA and psoriasis[7,8]. Linkage and association analyses have shown that the major histocompatibility complex (MHC) is the major genetic determinant related to PsA and psoriasis susceptibility[9]. The association between psoriasis and joint disease was first recognized by Alibert[10] and PsA was later defined as a seronegative inflammatory arthritis, divided into 5 phenotypes[11]. The pathogenesis of the disease is not fully clear, but genetic, environmental, and immunological factors are con-

From Taipei Medical University, Municipal Wan Fang Hospital; Section of Allergy, Immunology and Rheumatology, Department of Medicine, Taipei Veterans General Hospital; Institute of Clinical Medicine, National Yang-Ming University; National Taipei College of Nursing; Department of Dermatology, Taipei Veterans General Hospital, Taipei; and Buddhist Tzu Chi General Hospital, Hualien, Taiwan.

H-T. Liao, MD, Taipei Medical University–Municipal Wan Fang Hospital, Section of Allergy, Immunology and Rheumatology, Department of Medicine, Taipei Veterans General Hospital, and Institute of Clinical Medicine, National Yang-Ming University; K-C. Lin, MD, National Taipei College of Nursing; Y-T. Chang, MD, Department of Dermatology, Taipei Veterans General Hospital; C-H. Chen, MD; T-H. Liang, MD, Taipei Medical University–Municipal Wan Fang Hospital; W-S. Chen, MD; C-Y. Tsai, MD; C-T. Chou, MD, Section of Allergy, Immunology and Rheumatology, Department of Medicine, Taipei Veterans General Hospital; K-Y. Su, MD, Section of Allergy, Immunology and Rheumatology, Department of Medicine, Taipei Veterans General Hospital and Buddhist Tzu Chi General Hospital.

Address reprint requests to Dr. C-T. Chou, Division of Allergy, Immunology and Rheumatology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Road, Beitou District, Taipei, Taiwan 112. E-mail: b8201098@tmu.edu.tw

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sidered to play a role in development and perpetuation for the disease. Investigations comprising monozygotic and dizygotic twin and family studies provided strong evidence of the importance of genetic factors in PsA[12,13]. The prevalence of PsA is 5.5% in the relatives compared with an estimated 0.1% in the normal population[13]. Further, several studies reported linkage between specific HLA and PsA[14-18]. Divergent distributions of HLA were documented among different reports, suggesting that HLA distribution may depend upon ethnic origin[14,15]. Comparisons of different populations with different HLA profiles would be of value in identifying the candidate genes involved in PsA. The Chinese population in Taiwan included inhabitants of heterogeneous ethnic background. Our aim was to investigate and map the distribution of HLA classes I and II in ethnic Chinese (Han Chinese) patients with PsA and psoriasis, and to compare results with a healthy control population.

MATERIALS AND METHODS

Patients and controls. Within 3 years (2003-06), we consecutively recruited 91 patients with PsA (50 men, 41 women) and 80 with psoriasis (49 men, 31 women) with exclusively a Han Chinese background who visited the rheumatology outpatient clinic at Taipei-Veterans General Hospital. Psoriasis was diagnosed by an expert dermatologist, and PsA by a rheumatologist according to the classification criteria established by Moll and Wright[13]. Random blood donor controls (75 individuals) from the same ethnic background were included. For the patients with PsA and psoriasis, features including enthesitis and uveitis were evaluated. Pelvic and lumbar spine radiographs were performed in all patients. A questionnaire was designed to record the patients' demographic data and clinical characteristics. Written informed consent was obtained from all participants, and the protocol was approved by the local institutional review board.

Laboratory examinations. HLA class I and II (-A, -B, -Cw, -DR, -DQ) typing was performed using polymerase chain reaction sequence-specific oligonucleotide (PCR-SSO) genotyping methods (Dynal, UK).

Statistical analysis. Statistical analysis was carried out using the SPSS software. Demographic data and clinical characteristics were summarized as the mean ± standard deviation for continuous variables, and as proportions for categorical variables. The Pearson chi-square test and Fisher's exact test were used, as appropriate, to analyze group differences. p values were provisionally regarded as significant if they were less than 0.05. Bonferroni correction for multiple testing was applied where indicated. Odds ratio (OR) was used to measure the group differences on different HLA profiles[19]. The Genecounting program (v1.3) was applied for calculating the linkage disequilibrium (LD).

RESULTS

Demographic data and clinical characteristics in patients with psoriasis and PsA. The ratio of men to women was 1.28 (men 54.95%, women 45.05%) in 91 patients with PsA, and 1.58 (men 61.25%, women 38.75%) in 80 with psoriasis. The mean age at presentation of psoriasis was 23.69 ± 9.02 years. Among patients with PsA, the mean age at presentation of psoriasis and arthritis was 37.02 ± 11.63 and 41.36 ± 9.81 years, respectively. Of the 91 patients with PsA, the numbers and percentage of patients affected with arthritis in monoarthritis, oligoarthritis, and polyarthritis were 33 (36.26%), 49 (53.85%), and 9 (9.90%), respectively. Thirty-one (34.07%) patients with PsA had spondyloarthropathy by radiograph, and 63 (69.23%) patients with PsA had peripheral arthritis. Three (3.3%) patients with PsA had both axial joint involvement and peripheral arthritis. During the disease course, uveitis developed in 21 patients with PsA (23.08%) and in 7 with psoriasis (8.75%) (p = 0.02). Enthesitis was noted in 29 patients with PsA (31.87%; Table 1). The most common initial manifestations in patients with PsA were psoriatic skin lesions (68 patients, 74.73%), followed by peripheral arthritis (12 patients, 13.19%), axial joint involvement (9 patients, 9.90%), enthesitis (5 patients, 5.50%), and uveitis (2 patients, 2.20%).

Comparison of HLA genotyping between patients and controls. In some cases only 1 allele was identified, which may indicate that the individual was either homozygous for that allele or carried a previously unidentified allele. As the proportion of unidentified alleles was likely to be very low, these cases were considered to be homozygous for genotyped allele in all further analysis.

The comparisons of HLA alleles (HLA-A, -B, -Cw, -DR, -DQ) among 91 patients with PsA, 80 with psoriasis, and 75 controls are shown in Table 2 and Table 3. HLA-B*27 was significantly higher in patients with PsA (25.27%, OR 6.01) than in controls. Among patients with psoriasis, HLA-Cw*0602 was the most frequent allele (32.50%, OR 6.74), followed by HLA-DR*07, and HLA-A*30; these alleles were also significantly higher in patients with psoriasis when compared with healthy controls (p < 0.05), and there was a trend

Table 1. Demographic data and clinical characteristics in 91 PsA and 80 psoriasis patients.

Demographics/Clinical Characteristics	PsA, n = 91	Psoriasis, n = 80
Male, n (%)	50 (54.95)	49 (61.25)
Female, n (%)	41 (45.05)	31 (38.75)
Age at onset of disease, yrs	37.02 ± 11.63	23.69 ± 9.02
Disease duration, yrs	6.72 ± 3.81	4.63 ± 2.62
Uveitis, n (%)	21 (23.08)	7 (8.75)
Monoarthritis, n (%)	33 (36.26)	Nil
Oligoarthritis, n (%)	49 (53.85)	Nil
Polyarthritis, n (%)	9 (9.09)	Nil
Enthesitis, n (%)	29 (31.87)	Nil

Table 2. HLA (–A, –B, –Cw, –DR, –DQ) genes in 91 PsA patients and 75 controls (only those genes with crude p < 0.05).

HLA	PsA, n = 91	(%)	Controls n = 75	(%)	Crude p	OR	S/NS†
B*27	23	(25.27)	4	(5.33)	0.001	6.01	S
B*58	6	(6.60)	20	(26.67)	< 0.001	0.19	S
DR*17	6	(6.60)	14	(18.67)	0.017	0.31	NS

S: significant difference; NS: nonsignificant difference. † Correct p value by Bonferroni correction for multiple testing.

Table 3. HLA (–A, –B, –Cw, –DR, –DQ) genes in 80 patients with psoriasis and 75 controls (only those genes with crude p < 0.05).

HLA	Psoriasis, 80	(%)	Controls, 75	(%)	Crude p	OR	S/NS†
Cw*06	26	(32.50)	5	(6.67)	< 0.001	6.74	S
DR*07	22	(27.50)	3	(4.0)	< 0.001	9.10	S
A*30	13	(16.25)	1	(1.33)	0.001	14.35	S
A*01	11	(13.75)	2	(2.67)	0.013	5.81	NS
B*58	5	(6.25)	20	(26.67)	0.001	0.18	S
DR*17	4	(5.0)	14	(18.67)	0.008	0.23	S

S: significant difference; NS: nonsignificant difference. † Correct p value by Bonferroni correction for multiple testing.

in HLA-A*01 (crude p = 0.013). On the other hand, HLA-B*58 was more frequently detected in controls than in either PsA or psoriasis patients (p < 0.05). The prevalence of HLA-DR*17 was significantly higher in controls than in patients with psoriasis (p < 0.05), and there was also a trend of HLA-DR*17 in PsA (crude p = 0.017). After calculating the LD between HLA-Cw*06 and other markers including -A*30, -B*27, -B*58, -DR*07, and -DR*17 using the Genecounting program, the results were 0.375 (Cw*06/A*30), 0.000196 (Cw*06/B*27), 0.0049 (Cw*06/B*58), 0.401 (Cw*06/DR*07), and 0.004 (Cw*06/DR*17), and it seemed that there was no strong LD between HLA-Cw*06 and the other markers.

Comparison of HLA genotyping between PsA and psoriasis groups. Clinically, some psoriatic patients experience only skin lesions during their whole life, while a group of patients with psoriasis will suffer joint inflammation and develop PsA. We compared PsA and psoriasis patient groups to look for specific HLA alleles that may induce arthritis. We found that HLA-B*27 and HLA-Cw*12 were more common in patients with PsA, while HLA-DR*07 was significantly more prominent in patients with psoriasis (p < 0.05) (Table 4). Also, the prevalence of HLA-B*27 was significantly higher in patients with PsA with axial joint involvement and uveitis (Table 5).

DISCUSSION

In our study, patients with PsA had onset of psoriasis at a later age (> 10 yrs) than patients with psoriasis alone. The age of patients with PsA who had onset of psoriasis in our results is similar to a previous study[20], and with psoriasis alone was also compatible with Zhang, *et al*'s study in a Chinese population and Reich, *et al*'s study in Germany[21,22]. However, varied results of age of onset of diseases in different studies were found and this may be due to the genetic or ethnic differences between psoriasis and PsA, which may influence the early or late development of psoriasis.

Table 4. HLA (–A, –B, –Cw, –DR, –DQ) genes in 91 patients with PsA and 80 with psoriasis (only those genes with crude p < 0.05).

HLA	PsA, n = 91	(%)	Psoriasis, n = 80	(%)	Crude p	OR	S/NS†
B*27	23	(25.27)	4	(5.0)	< 0.001	6.42	S
Cw*12	22	(24.18)	3	(3.75)	< 0.001	8.18	S
DR*07	4	(4.40)	22	(27.50)	< 0.001	0.12	S
Cw*06	15	(16.48)	26	(32.5)	0.014	0.41	NS
Cw*08	8	(8.79)	17	(21.25)	0.021	0.35	NS

S: significant difference; NS: nonsignificant difference. † Correct p value by Bonferroni correction for multiple testing.

The aim of our study was to map the HLA alleles for susceptibility to psoriasis in patients with PsA by comparing the associations found in these patients to those of matched patients with psoriasis alone. Most patients with PsA have the classic psoriatic vulgaris pattern of skin lesion[23]. However, there are certain genetic differences between these 2 diseases, as the putative psoriasis gene is in LD with different HLA haplotypes in each form of the disease. In our study, several polymorphic markers spanning this region were studied and the overlap between PsA and psoriasis was analyzed. Most previous studies on class II HLA antigens in PsA have been performed using the serological technique. Because we determined HLA alleles by PCR-SSO genotyping method with decreased frequency of non-identified alleles, our results could diverge from those of others. The association with HLA antigens and disease expression varies and there are inconsistencies between studies[15,24-26]. The exceptions, apart from HLA-B*27 and axial disease, are the reports on HLA-Cw*0602, which have repeatedly been shown to determine early onset of psoriasis[27].

The significance of the association of various HLA alleles with PsA or psoriasis is difficult to interpret. Interpretation becomes particularly difficult if the association is primary to psoriasis (skin manifestation only) or secondary to an association with PsA (skin involvement with arthritis). An important question is why, if psoriasis and PsA are in association with the same susceptible locus, do the risk haplotypes differ between the 2 forms of disease. It is tempting to speculate that some of the alleles modify disease expression, rather than being involved in disease susceptibility. We are aware that the number of patients in our study was small. Despite this, several associations remain significant after correction for a number of comparisons. The high degree of polymorphism of the MHC, the sequence, and the presence of genes may vary between haplotypes. Therefore, it will be necessary to isolate the potential genes in the risk haplotypes in order to study their disease-associated polymorphism in any attempt to determine the exact position of the causative gene.

This is to our knowledge one of the most extensive studies involving comparison of HLA antigens and clinical features between PsA and psoriasis in a Chinese population. This applies both to the numbers of HLA-typed patients and controls and to the clinical measures that were analyzed. The Chinese population in Taiwan has maintained ethnic genetic-specific characteristics since ancient times. Comparisons of HLA in Chinese with Caucasian populations revealed the dif-

Table 5. The relationship between HLA-B*27-positive and axial joint involvement and uveitis in 91 patients with PsA.

	Axial Joint Involvement, n = 31	Peripheral Arthritis n = 63	Crude p	Uveitis, n = 21	No Uveitis, n = 70	Crude p	S/NS†
HLA-B*27 -positive (%)	15 (48.39)	8 (12.70)	< 0.001	10 (47.62)	8 (11.43)	< 0.001	S

† Correct p value by Bonferroni correction for multiple testing.

ferences that are important in determining the disease susceptibility genes in both PsA and psoriasis.

It has been established that the primary association of HLA genes in psoriasis was HLA-Cw*06 and HLA-DR*07[28-33]. Chang, *et al* studied Chinese patients with psoriasis in Taiwan, and found HLA-Cw*06 was also significantly higher in the psoriasis group than in the control group (18.6% vs 6.56%, respectively; $p < 0.005$)[34]. The HLA-B*38/HLA-Cw*12 in LD and HLA-DR*07 were more common in PsA[1,28,35]. The haplotypes contain genes that have been described as putative susceptibility factors for psoriasis. All the ancestral haplotypes, AH 13.1 (A*30;Cw*06;DR*07), AH 57.1 (A*01;Cw*06;DR*07), and AH 47.1 (A*03;Cw*06;DR*07), contained the HLA-Cw*06 and HLA-DR*07 alleles, which have been reported by various studies to be associated with psoriasis[36]. In Chan, *et al* and Kim, *et al*'s reports, HLA-A*01, HLA-A*30, HLA-Cw*06, and HLA-DR*07 were significantly elevated among patients with psoriasis in Chinese and Korean populations[37,38]. The unique HLA genes in psoriasis in our study (HLA-A*30, HLA-Cw*06, and HLA-DR*07) were also similar to those in previous studies. Although the frequency of HLA-B*27 is lower in PsA than in ankylosing spondylitis or reactive arthritis, it is still considered a predisposing factor to PsA and has consistently been noted to increase in patients with PsA compared with controls[1,17]. In several ways, our results differ from some of the known associations between HLA antigens and PsA/psoriasis, supporting our assumption that Chinese patients with PsA or psoriasis may present different HLA associations, which is possibly related to the varied ethnic origin (for instance, HLA-B16, -B17, -B27, -B39, -Cw6 in PsA and HLA-B17, -Cw6, -DR7 in Caucasian patients with psoriasis; HLA-A3, -B13, -B38, -DRB01, -DRB03 in Jewish patients with PsA; and HLA-A2, -B46, -DR8, and -B27 in Japanese patients with PsA)[15,20,39]. On the other hand, we also found some alleles including HLA-B*58 and HLA-DR*17 that appeared to protect from disease developing into either PsA or psoriasis. Although there were some distinct genetic differences betweens these 2 disorders, epidemiological and immunological evidence suggests that some determinants are likely to be shared between the 2 diseases. It is suggested that heterogeneous genetic predisposition may affect PsA and psoriasis. In our report, the HLA-B*27-positive PsA patients had more uveitis and axial joint involvement, and these results were similar to those of previous studies[15,16,40].

There is a clear genetic contribution to PsA and psoriasis. Some different genes in Chinese patients with PsA and psoriasis suggest that these patients present a different HLA distribution from Caucasians. Our study is limited by its relatively small number of patients, and further studies with larger populations are warranted.

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